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Outcome and Impact of Aortic Valve Replacement in Patients With Preserved LVEF and Low-Gradient Aortic Stenosis

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ABSTRACT

BACKGROUND Low mean transvalvular gradient (<40 mm Hg) and small aortic valve area (<1.0 cm^2) in patients with aortic stenosis (AS) and preserved left ventricular ejection fraction raises uncertainty about the actual severity of the stenosis and survival benefit of aortic valve replacement (AVR).

OBJECTIVES This study analyzed studies of mortality and survival impact of AVR in patients with low-gradient (LG) AS and preserved left ventricular ejection fraction, including paradoxical low-flow (i.e., stroke volume index <35 ml/m^2), low-gradient (LF-LG) and normal-flow, low-gradient (NF-LG), and those with high-gradient (≥40 mm Hg) AS or moderate AS.

METHODS Studies published between 2005 and 2015 were analyzed. Primary outcome was the survival benefit associated with AVR. Secondary outcome was overall mortality regardless of treatment.

RESULTS Eighteen studies were included in the analysis. Patients with LF-LG AS have increased mortality compared with patients with moderate AS (hazard ratio [HR]: 1.68; 95% confidence interval [CI]: 1.31 to 2.17), NF-LG (HR: 1.80; 95% CI: 1.29 to 2.51), and high-gradient (HR: 1.67; 95% CI: 1.16 to 2.39) AS. AVR was associated with reduced mortality in patients with LF-LG (HR: 0.44; 95% CI: 0.25 to 0.77). Similar benefit occurred with AVR in patients with NF-LG (HR: 0.48; 95% CI: 0.28 to 0.83). Compared with patients with high-gradient AS, those with LF-LG were less likely to be referred to AVR (odds ratio: 0.32; 95% CI: 0.21 to 0.49).

CONCLUSIONS Patients with paradoxical LF-LG AS and NF-LG AS have increased risk of mortality compared with other subtypes of AS with preserved left ventricular ejection fraction, and improved outcome with AVR. (J Am Coll Cardiol 2015;66:2594–603) © 2015 by the American College of Cardiology Foundation.

The American College of Cardiology/American Heart Association and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines generally recommend aortic valve replacement (AVR) in patients with severe aortic stenosis (AS) who have symptoms, left ventricular (LV) systolic dysfunction (i.e., left ventricular ejection fraction [LVEF] <50%), and/or undergo coronary artery bypass graft surgery or other heart surgery (1,2). These guidelines propose a peak aortic jet velocity >4.0 m/s, a mean transvalvular gradient >40 mm Hg, and/or an aortic valve area (AVA) <1.0 cm^2 as the criteria for identification of severe AS.

However, clinicians are sometimes confronted with patients with discordant findings, the most frequent being the combination of a measured small AVA (<1.0 cm^2) consistent with the presence of severe AS but a low mean gradient (<40 mm Hg) rather indicating the presence of moderate AS (MAS). This low-gradient (LG) AS entity may raise uncertainty

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regarding the actual severity of the stenosis and the potential indication for AVR if the patient is symptomatic. This entity is often related to the presence of low LV outflow. Indeed, given that the pressure gradient is directly related to the squared function of transvalvular flow rate, even a modest decrease in flow rate can lead to an important reduction in gradient and thus to an underestimation of stenosis severity. This low-flow, LG (LF-LG) condition may occur in the context of either a reduced (i.e., classical LF) or preserved (i.e., paradoxical LF) LVEF. However, such discordance may also be observed in patients with normal LVEF and flow, in which case it may be caused by measurement errors, a small body size, or previously emphasized inherent inconsistencies in the guidelines AVA/gradient criteria (3).

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According to current guidelines, AVR is recommended in: 1) symptomatic patients with high-gradient (HG) AS, regardless of their AVA, LVEF, or flow (Class I); 2) patients with classical (low LVEF) LF-LG after confirmation of stenosis severity by dobutamine stress echocardiography (Class IIa); or 3) symptomatic patients with paradoxical (preserved LVEF) LF-LG after confirmation of stenosis severity (Class IIa). The paradoxical LF-LG AS was described for the first time in 2007 (4) and the IIa recommendation for AVR in these patients was added in the 2012/2014 edition of the guidelines (2,5). The studies published before and after the publication of these guidelines have, however, yielded conflicting results with regard to the outcome and benefit of AVR in the patients with paradoxical LF-LG AS (6–11). Furthermore, the guidelines provide no specific recommendation for the symptomatic patients with preserved LVEF and normal-flow, LG (NF-LG) AS, although recent studies (12) suggest that an important proportion of these patients have severe AS.

The objective of this meta-analysis was thus to compare patients with LG AS and preserved LVEF, including paradoxical LF-LG and NF-LG, with those with HG AS or MAS with respect to overall mortality and impact of AVR on survival.

METHODS

A literature search was performed in PubMed, Embase, Ovid, and Google Scholar for studies published between 2005 and 2015 without language restriction according to the following criteria: "low gradient aortic stenosis" OR "paradoxical low flow low gradient aortic stenosis." The related articles function was used to broaden the search. The Cochrane library was also searched using the previously mentioned terms. All the review articles whose subject was LG AS and their reference lists were also reviewed.

INCLUSION AND EXCLUSION CRITERIA. Articles were included in the meta-analysis if they included any of the following:

1. Comparison of overall mortality in patients with LG (mean gradient <40 mm Hg with AVA <1.0 cm^2 and/or indexed AVA <0.6 cm^2/m^2) or LF-LG (stroke volume index <35 ml/m^2 and gradient <40 mm Hg with AVA <1.0 cm^2 and/or indexed AVA <0.6 cm^2/m^2) or NF-LG (stroke volume index >35 ml/m^2 and gradient <40 mm Hg with AVA <1.0 cm^2 and/or indexed AVA <0.6 cm^2/m^2) AS versus those with HG (gradient ≥40 mm Hg) or MAS (gradient <40 mm Hg with AVA >1.0 cm^2 and/or indexed AVA >0.6 cm^2/m^2). All groups have preserved LVEF and patients with classical (low LVEF) LF-LG AS were excluded from the analysis.
2. Observational comparison of AVR (either surgical aortic valve replacement [SAVR] or transcatheter aortic valve replacement [TAVR]) versus conservative management in patients with LG, LF-LG, or NF-LG AS. When the studies included in this meta-analysis reported outcome data of patients with HG AS according to treatment, AVR versus conservative management, these results were included and analyzed.

The following exclusion criteria were used to select the final articles for the meta-analysis: <20 patients in any group, and use of other criteria other than recommended by the American College of Cardiology/American Heart Association and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines (2,5) for the definition of severe and/or LG AS.

The study sites and inclusion were compared to ensure minimal patient overlap in different publications from the same site. If extensive overlap existed, only the publication with the largest or diagnostically most complete cohort (e.g., all patients instead of only patients with AS) was included. In case studies in which the outcome of AVR versus conservative treatment of patients with LG AS is analyzed separately from that of patients with LF-LG, both analyses were included and considered as different studies for the pooled analysis. LF (data for LF-LG) was added after the name of the author in the forest plots.

OUTCOMES. Primary outcome was the survival benefit associated with AVR in patients with LG,

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

CI = confidence interval

HG = high gradient

HR = hazard ratio

LF = low flow

LG = low gradient

LV = left ventricular

LVEF = left ventricular ejection fraction

MAS = moderate aortic stenosis

NF = normal flow

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

LF-LG, or NF-LG. The secondary outcome was the comparison of overall mortality, regardless of type of treatment, in patients with LF-LG, NF-LG, HG, and MAS. Data were obtained from unmatched populations in the included studies to get the real-life mortality risk of the patients with the different AS entities. The following variables were obtained to evaluate the surgical and cardiovascular risk of each group: prevalence of female patients, age, coronary artery disease, hypertension, diabetes, and renal failure.

STATISTICAL ANALYSIS. For each individual study, hazard ratios (HRs) reflecting long-term mortality along with their corresponding variances were calculated. When only the survival curves were available, these were inspected and the overall mortality rates were estimated using 6-month intervals using the method of Parmar et al. (13). Overall log HRs using inverse variances as weights were then calculated for each study. The odds ratio was used as the summary statistic for categorical variables. For continuous variables, the summary statistic chosen was the mean difference.

Because of patient and treatment procedure heterogeneity in the included studies, random effects model was used to calculate the summary statistics and their 95% confidence intervals (CIs). Meta-analyses results are displayed in forest plots. Analysis was conducted using Review Manager Version 5.2 (The Cochrane Collaboration, Update Software, Oxford, United Kingdom).

RESULTS

The search yielded 177 potential studies for analysis. Of these, 74 articles did not compare outcomes among groups as specified in the inclusion criteria, 34 articles were reviews or editorials, and 51 of them did not address specifically the topic of investigation or did not report the data required to analyze the primary or secondary outcomes of the present study. The final total number of studies included in the meta-analysis was 18 and the total number of patients was 7,459 (**Table 1**, **Figure 1**). None of these studies, except that of Herrmann et al. (14), which was a post-hoc analysis of the PARTNER-I (Placement of Aortic Transcatheter Valves I) trial, contained a randomized comparison of AVR versus conservative treatment. These articles comprised a total of 1,012 patients with MAS (59% were symptomatic, 35% underwent AVR), 3,056 patients with HG (75% symptomatic, 70% AVR), and 3,391 patients with LG AS (56% symptomatic, 58% AVR). Of the latter subset, 1,353 patients had LF-LG, 1,553 patients had NF-LG, and 581 patients had no definition of the flow status (LF vs. NF). Not all of the included articles reported both the primary and secondary outcomes specified previously (**Figure 1**).

OVERALL MORTALITY. Patients with LF-LG AS have increased global risk of death compared with patients with MAS (HR: 1.68; 95% CI: 1.31 to 2.17) and those with NF-LG (HR: 1.80; 95% CI: 1.29 to 2.51) (**Figure 2**). The LF-LG patients also had higher risk of mortality compared with those with HG AS (HR: 1.67; 95% CI: 1.16 to 2.39). When patients with HG are compared with those with NF-LG, no differences were found with regard to mortality (HR: 1.12; 95% CI: 0.89 to 1.42).

Only 2 of the included studies reported outcome data in HG AS versus MAS. As expected, both studies found that HG AS is associated with increased risk of mortality compared with MAS (Clavel et al. [6]: HR: 5.82; 95% CI: 3.92 to 8.64; Tribouilloy et al. [11]: HR: 1.74; 95% CI: 1.27 to 2.39).

SURVIVAL BENEFIT WITH AVR. In patients with LF-LG who undergo AVR, mortality was reduced by 56% (HR: 0.44; 95% CI: 0.25 to 0.77) (**Figure 3**). Similar survival benefit was obtained after AVR in patients with NF-LG (HR: 0.48; 95% CI: 0.28 to 0.83). When we included all studies that reported survival in LG AS irrespective of flow, patients who underwent AVR had reduced risk of overall mortality (HR: 0.44; 95% CI: 0.33 to 0.58). Patients with HG AS displayed the greatest survival benefit with AVR (HR: 0.25; 95% CI: 0.19 to 0.35). Compared with patients with HG AS, those with LF-LG were less likely to be referred to AVR (odds ratio: 0.32; 95% CI: 0.21 to 0.49) (**Figure 4**). Only 2 studies (6,11) reported data of AVR versus conservative management in patients with MAS and these 2 studies did not find any significant benefit of AVR on survival in these patients (Clavel et al. [6]: HR: 0.44; 95% CI: 0.17 to 1.12; and Tribouilloy et al. [11]: HR: 0.66; 95% CI: 0.36 to 1.22).

COMPARISON OF PATIENT BASELINE CHARACTERISTICS. Compared with patients with HG, those with LF-LG and those with NF-LG AS were older and had higher prevalence of coronary artery disease, diabetes, and hypertension (Online Figures S1 to S4). Patients with LF-LG had similar baseline characteristics compared with patients NF-LG (Online Figures S5 and S6).

Among patients with LF-LG AS, those who underwent AVR were older, were predominantly men, and had higher prevalence of renal failure (Online Figures S7 and S8).

DISCUSSION

The main findings of this meta-analysis are: 1) patients with LF-LG AS have higher risk of overall mortality

TABLE 1 Description of Included Studies

First Author, Year (Ref. #)	Criteria for the Definition of LF/LG	Number of Patients				SAVR/ TAVR	Symptomatic Status (%)
		HG (AVR%)	LF-LG (AVR%)	NF-LG (AVR%)	LG (AVR%)		
Pai et al., 2008 (16)	AVA ≤0.8 cm^2, MG <30 mm Hg				52 (35)	SAVR	ND
Belkin et al., 2011 (17)	AVA ≤1 cm^2, MG <30 mm Hg	67 (49)			94 (23)	SAVR	S (54), A (46)
Jander et al., 2011 (23)	AVA ≤1 cm^2, MG <40 mm Hg, SVI <35 ml/m^2		223 (41)	212 (43)	435 (42)	SAVR	A
Tarantini et al., 2011 (18)	AVA ≤1 cm^2, peak-to-peak gradient <30 mm Hg, SVI <35 ml/m^2		20	82	102 (72)	SAVR	S (88), A (12)
Clavel et al., 2012 (6)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2	187 (80)	187 (44)		187 (44)	SAVR	S (71), A (29)
Eleid et al., 2013 (21)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2	1299 (69)	53 (49)	352 (40)	405 (41)	SAVR	S (62), A (38)
Herrmann et al., 2013 (14)	AVA ≤0.8 cm^2, MG <40 mm Hg, SVI <35 ml/m^2		52 (44)		52 (44)	TAVR	S
Le Ven et al., 2013 (31)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2	195 (100)	86 (100)	110 (100)	196 (100)	TAVR	S
Mehrotra et al., 2013 (8)	AVA ≤1 cm^2, MG <40 mm Hg, SVI <35 ml/m^2		38	75	113		S (26), A (74)
Melis et al., 2013 (9)	AVA ≤1 cm^2, MG <40 mm Hg, SVI <35 ml/m^2	169 (66)	42 (45)	98 (53)	140 (51)	SAVR	ND
Mohty et al., 2013 (20)	AVA ≤1 cm^2, MG <40 mm Hg, SVI <35 ml/m^2	386 (94)	99 (84)	172 (87)	271 (86)	SAVR	S (89), A (11)
O'Sullivan et al., 2013 (33)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2	208 (100)	85 (100)		85 (100)	TAVR	S (71), A (29)
Ozkan et al., 2013 (7)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2		135 (40)	125 (55)	260 (47)	SAVR	S (93), A (7)
Grupper et al., 2014 (32)	AVA ≤1 cm^2, MG <40 mm Hg		113	303	416 (23)	SAVR	ND
Maes et al., 2014 (10)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2	144 (42)	115	90	205 (33)	SAVR	S (37), A (63)
Parikh et al., 2015 (34)	AVA ≤1 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2		536 (100)	152 (100)	688 (100)	SAVR	S (81), A (19)
Tribouilloy et al., 2015 (11)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2	247 (53)	57 (12)	85 (25)	142 (20)	SAVR	S (55), A (45)
Yamashita et al., 2015 (35)	iAVA ≤0.6 cm^2/m^2, MG <40 mm Hg, SVI <35 ml/m^2	154	19	61	80		S (46), A (54)

A = asymptomatic; AVA = aortic valve area; AVR = aortic valve replacement; HG = high-gradient; iAVA = indexed aortic valve area; LF-LG = low-flow, low-gradient; MG = mean gradient; NF-LG = normal-flow, low-gradient; ND = not determined; S = symptomatic; SAVR = surgical aortic valve replacement; SVI = stroke volume index; Symptom status = symptomatic status reported by authors; TAVR = transcatheter aortic valve replacement.

compared with those with MAS, NF-LG AS, and HG AS; 2) patients with NF-LG AS have higher risk of mortality compared with patients with MAS but similar risk compared with patients with HG AS; and 3) SAVR/TAVR improves overall survival in patients with LF-LG and in those with NF-LG AS (**Central Illustration**).

OUTCOMES AND IMPACT OF AVR IN PARADOXICAL LF-LG AS. A relatively large proportion (30% to 50%) of AS patients with preserved LVEF have LF (stroke volume index <35 ml/m^2) and because of the LF state, these patients often have a LG despite the presence of severe stenosis. The high prevalence of LF in the AS population is not necessarily surprising given that this population is predominantly elderly, with frequent comorbidities (systemic hypertension, coronary artery disease, diabetes, atrial fibrillation, mitral regurgitation, tricuspid regurgitation, mitral stenosis) and associated complications (pronounced LV concentric remodeling, impaired LV diastolic filling, ventricular dyssynchrony, impaired LV systolic longitudinal function). These comorbidities and associated complications may all contribute to reduce stroke volume and increase risk of mortality and morbidity. Accordingly, in most previous studies (4,6,8,15–22), patients with paradoxical LF-LG AS had worse symptomatic status and prognosis compared with those with MAS, NF-LG, or HG AS. However, some studies (10,11,23) found similar prognoses for LF-LG patients versus those with MAS, NF-LG, or HG AS.

LF-LG AS is a highly heterogeneous entity and the discrepancies between previous studies may be related to differences in the baseline characteristics of the study populations and in the Doppler-echocardiographic methods and definitions used to identify LF-LG AS (4,6–8,10,21,23–25). These factors may also explain why the prevalence of LF-LG AS

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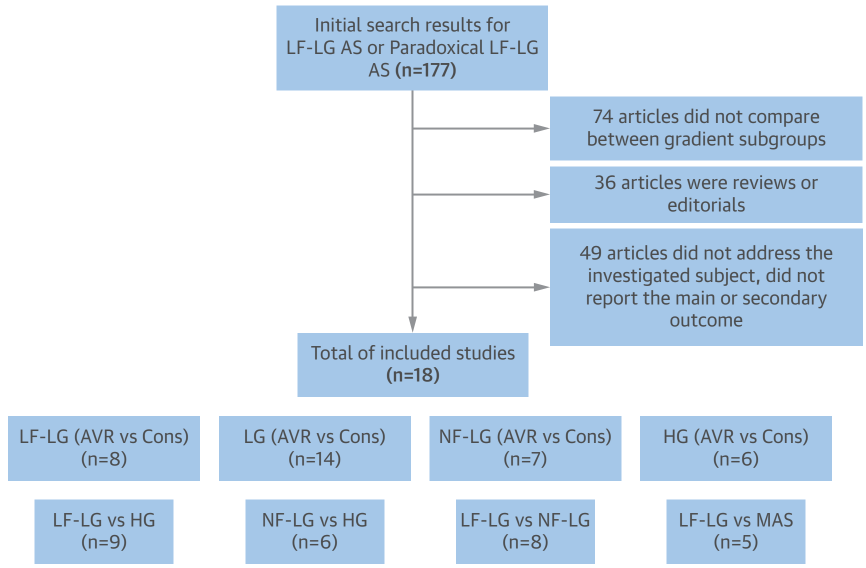
FIGURE 1 Flow Chart for Inclusion of the Studies



AS = aortic stenosis; AVR = aortic valve replacement; Cons = conservative treatment; HG = high-gradient; LF-LG = low-flow, low-gradient; LG = low-gradient; MAS = moderate aortic stenosis; NF-LG = normal-flow, low-gradient.

varies extensively from one study to the other (5% to 35%) (3,4,10,11,16,20,21,26).

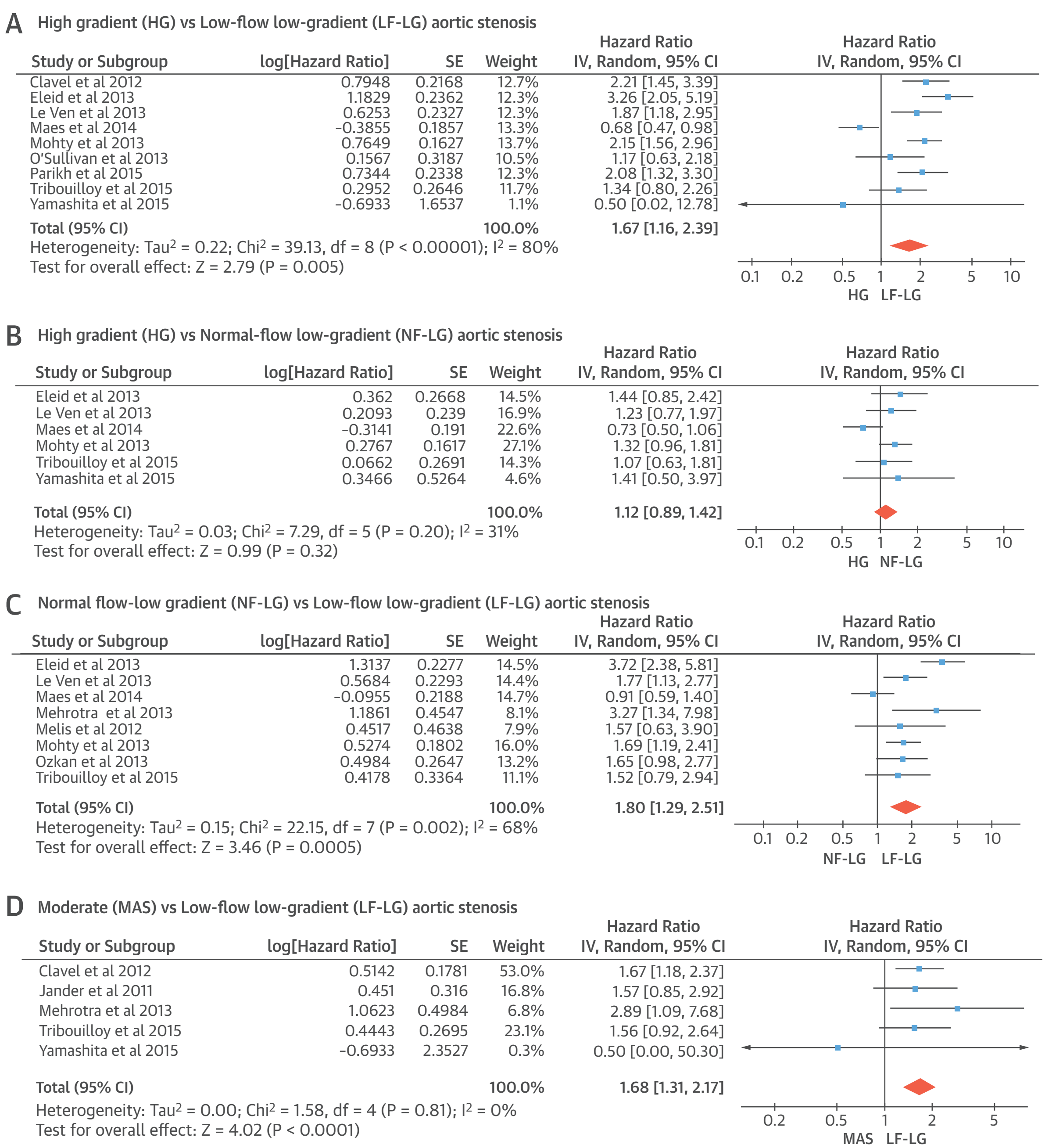
With low transvalvular flow, the forces applied against the valve cusps may not be sufficient to completely open a valve that is mildly or moderately stenotic. This "pseudosevere" AS phenomenon may occur with both classical and paradoxical LF-LG. Previous studies report that 30% to 50% of patients with paradoxical LF-LG AS have pseudosevere AS (12,27,28). Hence, discrepancies among previous studies with regard to the outcomes and survival benefit of AVR in patients with paradoxical LF-LG may also be, at least in part, related to differences in the proportion of patients with pseudosevere versus true severe AS included in each study. Nonetheless, the pooled analysis of the present study confirms that overall, paradoxical LF-LG AS is associated with increased risk of mortality compared with the other subtypes of AS with preserved LVEF. These findings also emphasize the importance of confirming the presence of severe stenosis before considering AVR in these patients, as recommended in the guidelines (2,5). Assessment of the morphological changes of the aortic valve (i.e., calcification, thickening) by transthoracic or transesophageal echocardiography, low-dose dobutamine stress echocardiography, or quantitative aortic valve calcium scoring by multidetector computed tomography may be used for this purpose (12,27,29).

The present study confirms that AVR is associated with a major survival benefit in patients with paradoxical LF-LG AS. Few studies (10,11,23) did not find a significant benefit of AVR, but most of these studies were underpowered for this specific analysis. The present study also confirms that patients with LF-LG are less often referred to AVR compared with those with HG AS. The presence of LG may result in underestimation of the stenosis severity and thus in underuse of AVR in patients with paradoxical LF-LG AS. This may have contributed to the increased risk of mortality observed in this subset.

Hence, the results of the present study provide further support to the Class IIa recommendation for AVR in symptomatic patients with paradoxical LF-LG severe AS.

OUTCOMES AND IMPACT OF AVR IN NF-LG AS. Although patients with NF-LG AS represent an important proportion (25% to 50%) of the AS population with preserved LVEF (3,7,8,11,21,30), the guidelines do not address the situation of these patients. As with LF-LG, NF-LG AS is also a highly heterogeneous entity that includes: 1) patients with errors in the measurement of the stroke volume, AVA, and/or gradient; 2) patients with small body size; and 3) patients with inconsistent grading. The latter category likely represents the largest proportion of the patients with NF-LG AS. From a fluid mechanics standpoint and if LV flow is normal, the cutpoint

FIGURE 2 Overall Mortality in the Different Subtypes of Flow/Gradient Aortic Stenosis



Comparison of risk of overall mortality in LF-LG versus HG **(A)**, NF-LG versus HG **(B)**, LF-LG versus NF-LG **(C)**, and LF-LG versus MAS **(D)**. CI = confidence interval; DF = degrees of freedom; IV = inverse variance; SE = standard error; other abbreviations as in Figure 1.

value of AVA of 1.0 cm^2 proposed in the guidelines to define severe AS indeed corresponds more precisely to a mean gradient around 30 to 35 mm Hg rather than to the 40 mm Hg cutpoint given in the guidelines (3). Hence, patients with NF-LG AS are generally in the moderate-to-severe stenosis range and, accordingly, recent studies (12) reported that about 50% of these patients may have hemodynamically severe stenosis. There are no data about the natural history of NF-LG AS. However, it is possible that some patients with

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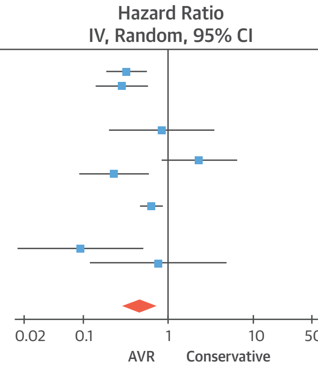
FIGURE 3 **Impact of Aortic Valve Replacement on Survival**

A Survival in patients with low-flow low-gradient (LF-LG) aortic stenosis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Belkin et al 2011	-0.7141	0.6902	0.0%	0.49 [0.13, 1.89]
Clavel et al 2012	-1.124	0.2758	17.9%	0.32 [0.19, 0.56]
Eleid et al 2013	-1.2448	0.3572	15.9%	0.29 [0.14, 0.58]
Grupper et al 2014	-0.6733	0.2707	0.0%	0.51 [0.30, 0.87]
Herrmann et al 2013	-0.7955	0.4066	0.0%	0.45 [0.20, 1.00]
Jander et al 2011	-0.1793	0.7269	8.5%	0.84 [0.20, 3.47]
Maes et al 2014	-0.7508	0.4079	0.0%	0.47 [0.21, 1.05]
Melis et al 2012	0.839	0.5269	12.0%	2.31 [0.82, 6.50]
Mohty et al 2013	-1.4697	0.4787	13.0%	0.23 [0.09, 0.59]
Ozkan et al 2013	-0.7133	0.2855	0.0%	0.49 [0.28, 0.86]
Ozkan LF	-0.4539	0.1668	20.3%	0.64 [0.46, 0.88]
Pai et al 2008	-0.9113	0.884	0.0%	0.40 [0.07, 2.27]
Tarantini et al 2011	-1.3243	0.3575	0.0%	0.27 [0.13, 0.54]
Tarantini LF	-2.3645	0.8725	6.7%	0.09 [0.02, 0.52]
Tribouilloy et al 2015	-0.2525	0.9529	5.9%	0.78 [0.12, 5.03]
Yamashita et al 2015	-1.3218	816.4965	0.0%	0.27 [0.00, Not estimable]
Total (95% CI)			**100.0%**	**0.46 [0.27, 0.79]**

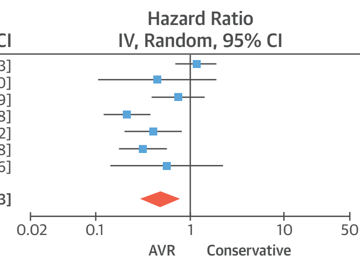
Heterogeneity: Tau² = 0.33; Chi² = 22.35, df = 7 (P = 0.002); I² = 69%
Test for overall effect: Z = 2.85 (P = 0.004)



B Survival in patients with normal-flow low-gradient (NF-LG) aortic stenosis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Eleid et al 2013	0.15	0.2591	17.7%	1.16 [0.70, 1.93]
Jander et al 2011	-0.8036	0.7382	8.4%	0.45 [0.11, 1.90]
Melis et al 2012	-0.3001	0.322	16.3%	0.74 [0.39, 1.39]
Mohty et al 2013	-1.5424	0.2938	16.9%	0.21 [0.12, 0.38]
Ozkan et al 2013	-0.9163	0.366	15.3%	0.40 [0.20, 0.82]
Tarantini et al 2011	-1.1548	0.3138	16.5%	0.32 [0.17, 0.58]
Tribouilloy et al 2015	-0.5638	0.7041	8.9%	0.57 [0.14, 2.26]
Total (95% CI)			**100.0%**	**0.48 [0.28, 0.83]**

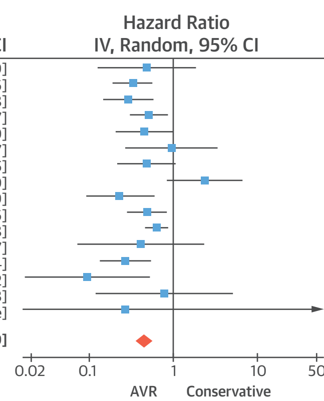
Heterogeneity: Tau² = 0.36; Chi² = 23.03, df = 6 (P = 0.0008); I² = 74%
Test for overall effect: Z = 2.65 (P = 0.008)



C Survival in patients with low-gradient (LG) aortic stenosis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Belkin et al 2011	-0.7141	0.6902	3.3%	0.49 [0.13, 1.89]
Clavel et al 2012	-1.124	0.2758	10.5%	0.32 [0.19, 0.56]
Eleid et al 2013	-1.2448	0.3572	8.2%	0.29 [0.14, 0.58]
Grupper et al 2014	-0.6733	0.2707	10.7%	0.51 [0.30, 0.87]
Herrmann et al 2013	-0.7955	0.4066	7.1%	0.45 [0.20, 1.00]
Jander et al 2011	-0.0535	0.6466	3.7%	0.95 [0.27, 3.37]
Maes et al 2014	-0.7508	0.4079	7.0%	0.47 [0.21, 1.05]
Melis et al 2012	0.839	0.5269	5.0%	2.31 [0.82, 6.50]
Mohty et al 2013	-1.4697	0.4787	5.7%	0.23 [0.09, 0.59]
Ozkan et al 2013	-0.7133	0.2855	10.2%	0.49 [0.28, 0.86]
Ozkan LF	-0.4539	0.1668	14.3%	0.64 [0.46, 0.88]
Pai et al 2008	-0.9113	0.884	2.2%	0.40 [0.07, 2.27]
Tarantini et al 2011	-1.3243	0.3575	8.2%	0.27 [0.13, 0.54]
Tarantini LF	-2.3645	0.8725	2.2%	0.09 [0.02, 0.52]
Tribouilloy et al 2015	-0.2525	0.9529	1.9%	0.78 [0.12, 5.03]
Yamashita et al 2015	-1.3218	816.4965	0.0%	0.27 [0.00, Not estimable]
Total (95% CI)			**100.0%**	**0.45 [0.35, 0.59]**

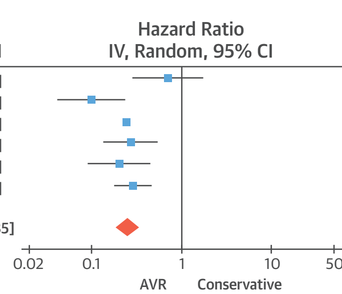
Heterogeneity: Tau² = 0.11; Chi² = 25.84, df = 15 (P = 0.04); I² = 42%
Test for overall effect: Z = 5.71 (P < 0.00001)



D Survival in patients with high-gradient (HG) aortic stenosis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Belkin et al 2011	-0.3532	0.4563	9.1%	0.70 [0.29, 1.72]
Clavel et al 2012	-2.3106	0.4353	9.7%	0.10 [0.04, 0.23]
Eleid et al 2013	-1.4036	0.0185	37.5%	0.25 [0.24, 0.25]
Maes et al 2014	-1.3096	0.3529	13.1%	0.27 [0.14, 0.54]
Melis et al 2012	-1.5845	0.4072	10.7%	0.21 [0.09, 0.46]
Tribouilloy et al 2015	-1.2379	0.2437	19.9%	0.29 [0.18, 0.47]
Total (95% CI)			**100.0%**	**0.25 [0.19, 0.35]**

Heterogeneity: Tau² = 0.07; Chi² = 10.37, df = 5 (P = 0.07); I² = 52%
Test for overall effect: Z = 8.69 (P < 0.00001)



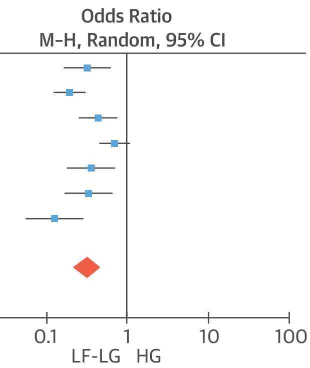
(A to D) Impact of AVR on survival in the different subtypes of flow/gradient aortic stenosis. Abbreviation as in Figures 1 and 2.

FIGURE 4 **Referral to AVR in Patients With LF-LG and HG Severe Aortic Stenosis**

Low-flow low-gradient (LF-LG) vs high gradient (HG)

Study or Subgroup	LF-LG Events	LF-LG Total	HG Events	HG Total	Weight	Odds Ratio M-H, Random, 95% CI
Belkin et al 2011	22	94	33	67	13.5%	0.31 [0.16, 0.62]
Clavel et al 2012	82	187	150	187	16.3%	0.19 [0.12, 0.31]
Eleid et al 2013	26	53	896	1299	15.1%	0.43 [0.25, 0.75]
Maes et al 2014	68	205	60	144	16.6%	0.69 [0.45, 1.08]
Melis et al 2013	19	45	112	166	13.5%	0.35 [0.18, 0.69]
Mohty et al 2013	83	99	363	386	13.4%	0.33 [0.17, 0.65]
Tribouilloy et al 2015	7	57	131	247	11.6%	0.12 [0.05, 0.28]
Total (95% CI)		**740**		**2496**	**100.0%**	**0.32 [0.21, 0.49]**
Total events	307		1745			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 22.50$, df = 6 (P = 0.0010); $I^2 = 73\%$
Test for overall effect: Z = 5.16 (P < 0.00001)

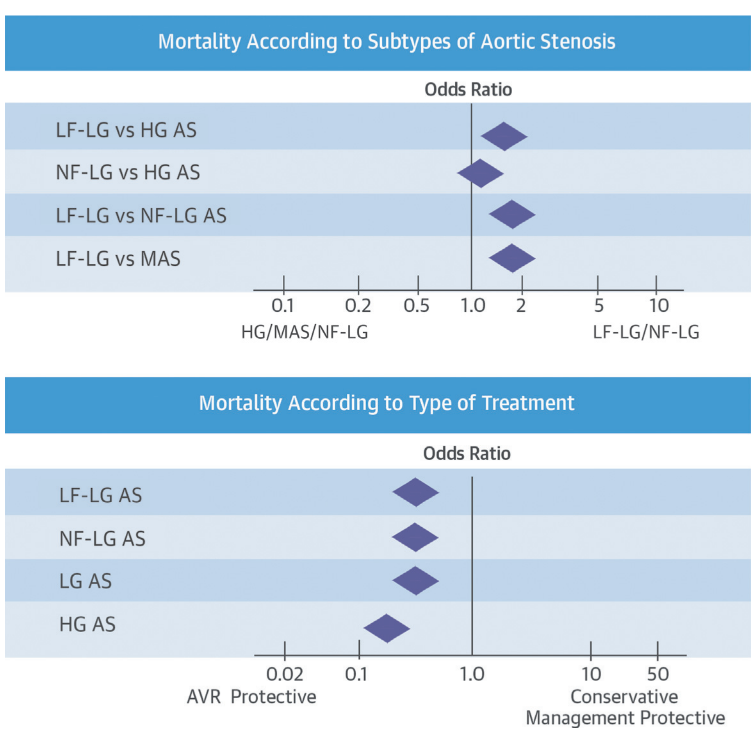


M-H = Mantel Haenszel; other abbreviations as in Figures 1 and 2.

NF-LG AS may progress to HG AS, whereas others may evolve to LF-LG AS.

The present meta-analysis reveals that the outcome of the patients with NF-LG AS is similar to that of patients with HG AS and better compared with patients with LF-LG AS. Furthermore, AVR was associated with improved survival in patients with NF-LG. Hence, in light of these results, confirmation

CENTRAL ILLUSTRATION **Outcome and Impact of Aortic Valve Replacement in the Different Subtypes of Flow/Gradient Aortic Stenosis**



Dayan, V. et al. J Am Coll Cardiol. 2015; 66(23):2594–603.

Pooled odds ratio for the different groups and modalities of treatment. AS = aortic stenosis; AVR = aortic valve replacement; HG = high-gradient; LF-LG = low-flow, low-gradient; LG = low-gradient; MAS = moderate aortic stenosis; NF-LG = normal-flow, low-gradient.

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of stenosis severity with additional diagnostic tests should probably be considered in patients with NF-LG AS who are symptomatic.

STUDY LIMITATIONS. We did not use individual data, therefore results and conclusions drawn from meta-regression analysis regarding independent predictors should be interpreted cautiously. In the context of a meta-analysis, it is generally not possible to obtain individual data. It is therefore impossible to adjust the analyses of outcomes for potential confounding variables. In particular, it was not possible to assess the impact of symptomatic status on outcomes and benefit of AVR in the different subtypes of AS.

Observational comparisons of AVR with conservative treatment were nonrandomized and therefore subject to confounding by indication bias. In particular, some patients with severe AS and severe comorbidities may have been considered at too high risk for AVR and therefore left on conservative management. This bias may thus have overestimated the benefit of AVR.

CONCLUSIONS

Patients with paradoxical LF-LG AS have increased risk of mortality compared with all other subtypes of severe AS with preserved LVEF, and their outcome is improved by AVR. These findings support the guidelines recommendation (Class IIa) for AVR in these patients when they are symptomatic and when severe stenosis is the most likely cause of symptoms. Furthermore, patients with NF-LG also had similar risk of mortality compared with those with HG AS and their outcome was improved by AVR. These findings suggest symptomatic patients with NF-LG should also receive particular attention and that additional diagnostic tests should be considered in these patients to corroborate the stenosis severity and determine the indication for AVR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with paradoxical low-flow, low-gradient severe AS and preserved LV ejection fraction have higher risk of mortality compared with other aortic stenosis subtypes.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: AVR improves survival in patients with paradoxical low-flow, low-gradient and in those with normal-flow, low-gradient severe AS.

TRANSLATIONAL OUTLOOK: Further studies are needed to understand the pathophysiological mechanisms responsible for low-gradient severe AS and derive improved methods for clinical risk stratification for patients with this condition.

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KEY WORDS aortic valve replacement, low gradient aortic stenosis, paradoxical flow aortic stenosis

APPENDIX For supplemental figures, please see the online version of this article.